tube every four hours to about one-third of its capacity or less with Dakin's solution. At the end of two hours another long tube is attached to the tube in the chest and the fluid siphoned out, the patient meanwhile lying on the sound side with the chest opening uppermost, or as nearly so as possible. The patient is told to pant or cough slightly at frequent intervals as long as the fluid remains in the chest, and by this means splash the fluid about inside the cavity, and so bathe with it the entire infected surface and any recesses that may exist.

In this way the pleural cavity contains for two hours a large quantity of sodium hypochlorite solution and is more or less empty for a like time. During the former period the patient lies rigidly on the sound side, without any raising of the shoulders, to prevent escape of the fluid and consequent flooding of the bed; during the latter he is free to lie as he chooses. Thus the patient gets a reasonable amount of rest and comfort and is saved the exhaustion associated with the maintenance of one constant position. In addition, once daily, the tube is removed, sterilized, and replaced, and the cavity washed out as in the usual treatment for empyema. To overcome the disadvantage of injecting cold fluid into the chest, I have found that it is better to make the Dakin's solution of double strength and, prior to filling, to dilute it with an equal quantity of warm sterile water.

If the original wound and site of fracture lie sufficiently far forwards, advantage is taken of this site for the insertion of the tube.

Sometimes difficulty is met with in siphoning out the fluid; this may be due either to the tube that is connected to the tube in the chest not being first filled with liquid or else to air being unable to enter the pleural cavity; in the latter case, it is well to slip an open-ended Carrel tube into the chest alongside the first. When this is done I use the smaller tube for filling up the pleura, as then the liquid cannot be injected too quickly.

When treatment is carried out in this way, it is found that pus formation and offensive odour largely disappear at the end of thirty-six hours and are absent at the end of three to four days; the patient's tongue becomes clean and moist almost at once; delirium and emaciation, so frequently seen in these cases, are absent, and the temperature and pulse rates fall much more rapidly than usual; indeed when looking at them, it is hard distinguish these cases from those that are not infected.

If pus continues to form under this method of treatment, it appears to be due to one or more of the following causes:

1. The Dakin's solution is not of proper strength or is used in insufficient quantity.
2. The cavity is not regularly filled and emptied.
3. A loculated cavity exists which the fluid does not reach.
4. A foreign body or loose bone fragments still remain in the pleural cavity.
5. Sloughing or abscess formation is taking place in the lung substance.

After using this method of treatment on a number of cases I have found that it is superior to other methods of treatment that I have tried. The benefit derived from it can easily be demonstrated by the rapid diminution of the number of organisms per field of the microscope in films made from the surface of the pleura. By this method, too, it is comparatively easy to raise the pleural cavity to "suture standard" and sew up the wound at an early date, with the result that lung expansion becomes more perfect and pleural thickening is largely avoided. I think another great advantage is that cross infection of the empyema cavity from without is avoided.

It is only recently that vitiligo, or leucoderma, has been associated with syphilis. E. M. Auer (*Amer. Journ. Med. Sci.*, Phila., 1917, vol. cliv, pp. 592-596) gives about a dozen references from literature to this subject, and quotes Zelenev's analysis of 52 cases of leucoderma with the conclusion that, etiologically, they fall into two groups—tuberculous and syphilitic. Auer also reports four cases of leucoderma in patients with late syphilitic lesions of the central nervous system, and draws attention to the early appearance of leucoderma as compared with the other symptoms; he points out also that the symmetrical and segmental distribution of the areas of leucoderma suggests a lesion of the central rather than of the peripheral nervous system.

THE ENDOTOXIN OF THE MENINGOCOCCUS

A METHOD OF EXTRACTING IT FOR THE PURPOSE OF STANDARDIZING ANTIMENINGOCOCCUS SERUM.

BY

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Few who have studied acute cases of cerebro-spinal fever during an outbreak can fail to be impressed by the potency of the toxin of the meningococcus, and if the observer is a bacteriologist he may be struck also by the relative infrequency with which this micro-organism is to be cultivated from the blood of the patients. Although the meninges are one of the chief sites of infection, a further feature of the disease that calls for notice is the relatively large number of pus cells that it may be necessary to search in film preparations of the cerebro-spinal fluid before one is found that contains meningococci. While there are occasional and striking instances in which the meningococcus is detected in large numbers in the cerebro-spinal system, or in the blood, in many cases of cerebro-spinal fever actual proliferation of the meningococcus in the tissues of the patient appears to be limited. Nor is this relatively restricted proliferation apparent only in cases that recover; even in fatal cases bacteriological investigation after death may reveal that the degree of meningeal suppuration is out of all proportion to the number of cocci present either in films or cultures of the meningeal exudate. There is little doubt that this limited proliferation of the meningococcus is often apparent rather than real, owing to the autolytic tendency of the coccus as well as to the lytic action of the secreted body fluids, both of which tend to liberate its endotoxin. In this relation it is of interest to recall that during the classical researches in course of which he reproduced the essential lesions and symptoms of cerebro-spinal fever in monkeys, and studied the fate of this micro-organism when introduced into the peritoneal cavity of guinea-pigs, or into the spinal canal of monkeys, Flexner observed this same point, and remarked that multiplication on the part of the cocci is not at all essential to the production of the peculiar symptoms and lesions: the meningococcus causing death by a poison liberated from the bacterial bodies.

For the purpose of comparing the pathogenic value of the meningococcus when alive, and when all chance of proliferation is eliminated, a series of experiments has been undertaken, and is still in progress, at the Central Cerebro-spinal Fever Laboratory. In the first place, three specimens of meningococcus were selected of definite pathogenicity to the mouse when introduced alive into the peritoneal cavity of that animal; and the effect on their individual pathogenicity was determined by killing the coccus by ether and then evaporating the warm broth suspension containing it to dryness *in vacuo* at 37° C. A series of falling doses of the suspension of living cocci was injected intraperitoneally into mice, and then duplicates of these doses were etherized, dried *in vacuo*, and next day (or later) redissolved by grinding up in distilled water, and, cultures having been taken to prove that the meningococcus was dead, injected intraperitoneally into mice. Proceeding in this way, it was found that, in the case of two of the meningococci, the coccus was fatal to the mouse in a smaller dose when alive than when killed in the manner described. In the case of the third meningococcus, however—which was a specimen of Type II recently isolated from a rapidly fatal case of cerebro-spinal fever—the coccus was fatal to mice in the same dose when killed, dried, and dissolved in the manner described, as when alive. While it would appear, therefore, that in the case of this particular meningococcus the endotoxin was either exceptionally potent, or more easily extracted than usual, the observation nevertheless furnishes a striking illustration of the great pathogenic importance of the endotoxin of this micro-organism.

It is generally agreed that exotoxin is not formed by the meningococcus in culture. On several occasions virulent specimens of the meningococcus have been cultivated at the Central Laboratory, in flasks of broth enriched by horse serum or by diluted rabbit's blood, and after incubation at 37° C. for a time, varying from a fortnight to a month, a portion of the broth was removed, the cocci contained by

it thrown down by centrifuge, and the clear supernatant fluid injected intraperitoneally into mice. In all cases the mice remained unaffected, so that no evidence has been obtained of the presence of soluble toxin in such cultures.

Up to the present two methods have been employed to obtain a solution of the endotoxin of the meningococcus. The first of these, which is the method favoured by Flexner and Dopfer, makes use of the autolysin of the meningococcus for the purpose of disintegrating the coccus, and setting free its endotoxin. All that is necessary is to make a suspension in saline of a young culture of the meningococcus, then to add some disinfectant such as toluol, and to leave the suspension at 37° C. The cocci undergo autolysis, and a proportion of their endotoxin passes into solution. The second method has been used by Kolle and Wassermann, Kraus, and others. Young cultures of the meningococcus are suspended in distilled water, or in decinormal soda solution, and submitted to agitation for several days in a shaking machine. The suspension is then centrifuged, and the clear supernatant fluid is found to contain endotoxin in solution. It is decanted, phenolated, and kept in the dark in the ice chest.

Neither of these methods would seem to be entirely satisfactory. The autolysate is open to the suspicion that during the process of lysis the toxin may be altered. The "shake extract" is obviously an incomplete procedure. The first step, therefore, in the present investigation was to attempt to find an improved method for the purpose of extracting its endotoxin from the meningococcus.

Besredka's Method of Extracting Endotoxin.

An examination of the literature on the subject of endotoxin soon showed that a method that was likely to be of service was that introduced by M. Besredka, of the Pasteur Institute, in 1905, and used by him and others since with much success for extracting their respective endotoxins from *B. pestis*, *B. dysenteriae*, *B. typhosus*, *B. diphtheriae*, *B. influenzae*, *Micrococcus melitensis*, gonococcus, etc. The method, however, does not appear to have been applied previously to the meningococcus. The procedure of Besredka is as follows:

The growth is removed from numerous cultures of the organism and dried *in vacuo* over sulphuric acid. The dry deposit is then scraped off, reduced to powder in a mortar, and stored in a dry place in the dark. This material Besredka calls "solid endotoxin," and it is found as a rule to be exceedingly toxic to animals. To extract the soluble toxin from it, a weighed amount of the solid endotoxin is mixed with a definite quantity of salt and ground up by hand in an agate mortar most carefully and thoroughly. When the mixture of dried bacteria and salt has been reduced to an impalpable powder, distilled water is added drop by drop, grinding the while, until the proportion of salt present is that of normal saline. The whole process takes about an hour, and at the end the mixture is allowed to stand, and if necessary is centrifuged until all detritus has settled to the bottom. The supernatant fluid, which is slightly opaque, is then removed and its toxicity determined in the usual manner.

In applying this method to the meningococcus a few modifications have been made. In the first place, as the result of comparative trials in which the degree of disintegration of the coccus was followed microscopically, and the toxicity of the extract determined on mice, I have abandoned the salt and use sterile sand instead, the extract being made entirely with distilled water. The procedure is as follows:

A meningococcus is selected of known serological type, and of such pathogenicity that one-tenth part of an eighteen hours' slope culture on tryptic agar when injected intraperitoneally into a mouse produces death within forty-eight hours. Such a culture being available, as many Petri dishes as possible of ordinary tryptic agar are inoculated with it and incubated for eighteen hours at 37° C. It is hardly advisable to work with less than fifty of such plates at a time. To remove the growth, 2 c.cm. of saline is poured on each plate, the growth is then raked off by a bent iron wire, and the suspension poured into a sterile test tube. A film preparation is made from each tube, stained by Gram and examined microscopically in order to exclude possible contaminations. The pure suspensions are mixed and centrifuged at top speed for an hour or more until the bulk of the cocci have been deposited. The top fluid is then thrown away, and the sediment of cocci evacuated into a Petri dish, 5 per cent. of ether added, and the dish placed with the cover off in a desiccator the bottom of which contains sulphuric acid. This desiccator is already connected to a manometer, and also to a powerful vacuum hand pump, designed and made for me some years ago by Mr. Fleuss of the Pulsometer Company. After receiving the dish, the desiccator is exhausted until a minus pressure of about 70 cm. of mercury has been obtained;

the tap is then closed, the desiccator disconnected, and placed in the incubator at 37° C. overnight. Next morning the contents of the Petri dish are seen to be quite dry; the dish is taken out, the deposit scraped off, reduced to powder in a mortar, and examined microscopically. The powder consists entirely of dried bodies of meningococci. It is weighed and stored in a glass-stopped bottle kept in a dry cupboard in the dark.

Before a desiccator is used for this purpose trials must be made to see how much water it will absorb in a night at 37° C. after being exhausted; and care must always be taken to ensure that the suspension of sedimented cocci placed in the Petri dish does not exceed this quantity. The ether is added to prevent the growth of air contaminations, which at first gave much trouble. Once the apparatus is in good working order, the manufacture of dried coccus proceeds without hitch; but microscopical examination both of the suspensions from the plates, and of the dried end-product, must never be omitted. We have found that by this method a hundred ordinary plates of meningococcus yield on an average about 1.8 grams of dried cocci.

Mode of Extracting the Soluble Endotoxin from the Dried Cocci.

A solution of the endotoxin is prepared in the following manner:

0.1 gram of the dried cocci is weighed out and placed with an equal amount of sterilized sand in an agate mortar. The mixture is carefully and thoroughly ground up by hand until the whole has been reduced to an impalpable powder. This generally takes about half an hour. Sterile freshly distilled water is then added drop by drop, and the grinding continued for another half-hour, until 5 c.cm. of distilled water has been added. The mixture is next poured off into a graduated centrifuge tube, and the amount made up to 5 c.cm. if any loss has occurred through evaporation. The tube is stood overnight in the ice chest, and next morning centrifuged at top speed until all detritus has settled to the bottom. The opaque supernatant fluid, which has an appearance somewhat resembling that of concentrated lemonade, is then decanted. This is the standard extract. If it is to be used for rabbits, 0.5 per cent. of phenol may be added, but if for mice intraperitoneally, phenol is better avoided, and a few drops of ether added as a preservative.

When larger amounts are required, successive lots of the dried coccus and sand are ground up and the aqueous extracts mixed.

Toxicity of the Dried Meningococcus and of its Aqueous Extract for Laboratory Animals.

The following are the results in mice and rabbits:

1. *Mice.* It has been found that the dried and powdered meningococcus prepared in the manner described is fatal to mice intraperitoneally in a dose varying from 2 to 10 mg. The results are generally quite regular, provided that the powder is ground sufficiently fine. For purposes of testing samples of serum, chief use has been made of the aqueous extract, the toxicity of which is always determined in duplicate, and the lowest dose at which both mice succumb within forty-eight hours taken as the M.L.D. Mice submitted to the action of the endotoxin of meningococcus become extremely prostrated, and their appearance suggests that the toxin has a direct action on their central nervous system. A proportion of these mice develop diarrhoea. *Post mortem* the right heart is usually dilated, and the spleen is often much enlarged.

2. *Rabbits.* When injected intravenously into rabbits the aqueous extract of the dried coccus seems to act in exactly the same manner as a large dose of the living meningococcus. From some observations carried out in conjunction with Major A. S. G. Bell, it would appear that when a rapidly fatal dose either of the living meningococcus or of the aqueous extract of the dried coccus is administered intravenously to these animals the temperature falls continuously until death, which may be ushered in by convulsions. A similar lowering of temperature was observed by Flexner in guinea-pigs that received a fatal dose of the living coccus intraperitoneally. Rabbits that die from an intravenous injection either of the living coccus or of the aqueous extract of the dried coccus often show *post mortem* petechial haemorrhages. These are especially frequent under the skin, and are thus similar to the subcutaneous haemorrhages seen in some acute cases in man of cerebro-spinal fever.

The aqueous extract of the dried meningococcus contains a considerable proportion of the bacterial protein in solution as well as the toxin. This is evident from the fact, amongst others, that extracts made in the same way from non-virulent meningococci, while containing the coccal endoprotein in solution, show a relatively small amount of endotoxin.

The extract of the dried coccus prepared in the manner described has recently been found to contain a substance lytic for the red blood corpuscles of man and also of the rabbit, mouse, and guinea-pig. From present observations, this substance appears to withstand heating for

half an hour to 60° C., though haemolysis may be delayed by the treatment. The haemolytic substance is present in extracts of the dried bodies of specimens of all four types, and observations are now in progress to determine (1) whether it is the same in all of them, or not; (2) whether it forms, as seems possible, an index to the degree of disintegration of the coccus; and (3) whether the presence of antihæmolyisin in antimeningococcus serum does, or does not, form an index of the presence of anti-endotoxin.

Some further experiments are in progress with a view to determining whether its charge of endotoxin can be increased by passing the meningococcus through a succession of mice. A number of meningococci have been passed through mice without increasing their virulence. In the case of one meningococcus, however—a specimen of Type I from a fulminating case—it was found that, after passage through five mice in succession, the virulence of the living coccus for the mouse had increased tenfold; but, in spite of this increase in virulence for the mouse, no increase could be detected in the amount of endotoxin for that animal contained by the coccus when dried and extracted. This result is of considerable interest because it suggests that, in addition to the charge of endotoxin, another factor may be concerned in the virulence of the meningococcus. The matter is at present being investigated by Dr. C. Shearer, F.R.S.

The antigenic value of the aqueous extract of the dried meningococcus is at present under investigation at the Central Laboratory. From present results it would appear to be serologically specific in much the same manner that the whole coccus is when injected into an animal such as the rabbit.

The Anti-endotoxic Value of Current Examples of Antimeningococcus Serum Supplied for Therapeutic Use.

By extracting their endotoxin in the manner described Besredka and his colleagues have been able to define the anti-endotoxic value of serums prepared against the micro-organisms of bacillary dysentery, plague, and typhoid respectively. It was found that in the case of the particular serums examined by him 1 c.cm. of the antidyentery serum neutralized 2,400 lethal doses of the dysentery endotoxin; 1 c.cm. of the antiplague serum neutralized 200 lethal doses of the plague endotoxin; and 1 to 2 c.cm. of the antityphoid serum neutralized 30 lethal doses of the endotoxin of the typhoid bacillus.

The anti-endotoxic value of antimeningococcus serum has been determined by Dopter and also by Wassermann, Kraus, and their co-workers. Dopter, who used an autolysate for this purpose, considers, as a result of his observations, that 1 c.cm. of antimeningococcus serum suitable for clinical use should neutralize five lethal doses of endotoxin. As a result of the observations of Wassermann and Leuchs, Kraus, and others, who used "shake extracts," it has been laid down that 1 c.cm. of antimeningococcus serum suitable for therapeutic use should neutralize four lethal doses of meningococcus endotoxin. The subdivision of the meningococcus group into a number of serologically distinct types had not been effected at the time when these observations were made.

Now the anti-endotoxic standard laid down for antimeningococcus serum by these observers cannot be regarded as anything but low in comparison with the anti-endotoxic values found by Besredka in case of the three antibacillary serums. Since there is at present no evidence, so far as I am aware, that the endotoxin of the meningococcus is more toxic to the horse than the powerful endotoxins of plague or dysentery, it would seem probable that the relative scarcity of anti-endotoxin in antimeningococcus serum is due to some special difficulty in the case of the meningococcus that has not yet been defined and overcome. For reasons given later the cause is most likely to lie in the form of meningococcus antigen used for preparing the horses. Some preliminary experiments upon this subject will be mentioned.

The method which I have used for testing antimeningococcus serums in respect of their content of anti-endotoxin is as follows:

All the serums are examined in duplicate, and in addition to the specimens of antimeningococcus serum for trial, a control is always carried out with normal horse serum. Two sterile watch-glasses are put out for each serum, and every watch-glass is enclosed in a Petri dish. With a 1 c.cm. pipette, graduated

in tenths, the M.L.D. of endotoxin is measured out into each watch-glass. A measured amount of serum is then added, the covers are replaced, and the Petri dishes placed for thirty minutes in the incubator at 37° C. in order to allow the endotoxin and anti-endotoxin to unite. When taken out of the incubator, many of these serums are seen to have produced an excellent precipitin reaction, which, however, by no means necessarily implies the presence of anti-endotoxin. The contents of the watch-glasses are then injected intraperitoneally each into an individual mouse. The mice are placed in sets of stalls specially designed for the purpose by Major T. G. M. Hine, and are kept under observation for three days.

TABLE I.—*Details of an Experiment in which Five Specimens of Antimeningococcus Serum were Tested against a Minimal Lethal Dose of Endotoxin of Type I and Type II Meningococcus respectively.*

Serum.	Amount.	Type I Endotoxin.	Result.	Type II Endotoxin.	Result.
Normal	0.5	0.2	+	0.2	+
	"	"	+	"	+
A.	0.5	0.2	+	0.2	+
	"	"	+	"	+
B.	0.5	0.2	—	0.2	+
	"	"	—	"	—
C.	0.5	0.2	—	0.2	—
	"	"	—	"	—
D.	0.5	0.2	+	0.2	—
	"	"	+	"	—
E.	0.5	0.2	+	0.2	—
	"	"	+	"	—

+ = Mouse died.

It is clear that in the dose tested (0.5 c.cm.), serum A, in spite of having an excellent amount of precipitin, agglutinin, and, from Captain Tulloch's observations, of opsonin also for the two commonest types of the meningococcus, is deficient in anti-endotoxin to Type I and weak in this antibody to Type II. Serum B, which gave excellent clinical results two years ago, still contains anti-endotoxin to Type I, but is now weak in this antibody to the endotoxin of Type II. Serum C, recently made by pooling the serums of univalent horses, has anti-endotoxin to both these types of the meningococcus. The two remaining serums only neutralize the endotoxin of Type II in the amount tested—namely, 0.5 c.cm.

Now this result cannot be considered satisfactory. The horses providing the serum had received numerous injections of cultures of current meningococci, yet a proportion of these samples of their serum put up for therapeutic use fails to show an appreciable amount of anti-endotoxin for one or other of the two commonest types of the meningococcus in 0.5 c.cm. As the cause almost certainly lies in the kind of antigen used for preparing the horses, a series of observations is now in progress for the purpose of defining the relative value of various preparations of the meningococcus for stimulating the production of anti-endotoxin.

As a preliminary measure the matter is being worked out on rabbits, and if successful, it is hoped, with the co-operation of those who are preparing antimeningococcus serum, to apply the result to horses at present in course of immunization against the meningococcus.

In the first place an investigation was made of the anti-endotoxic value of the serum of a set of rabbits already in course of immunization at the Central Laboratory. Two of these animals had been prepared for over six weeks against first killed, and then living cultures of meningococcus Type I (strain Littledale). Two more had been under similar treatment for the same period against living cultures of meningococcus Type II (strain Harrison). All these rabbits stand intravenously the whole of the growth of an eighteen hours' slope culture of these respective meningococci without more than temporary loss of weight, and without marked symptoms; and their blood contains a good yield of agglutinin for the homologous coccus; yet none of the rabbits contain enough anti-endotoxin in 0.5 c.cm. of their serum to neutralize one lethal dose of endotoxin of the homologous type of meningococcus. Now neither of the meningococci injected into these rabbits is particularly virulent for the mouse—the fatal dose for the mouse intraperitoneally being from one-half to the whole of an eighteen hours' slope culture, and also the dried bodies of the particular meningococci in question have been found to yield but little endotoxin. Some more rabbits, therefore, are at present under immunization with further samples of meningococci of the same two types, but of higher virulence for the mouse, and giving a good yield of endotoxin in aqueous extracts of their

dried bodies. At the same time, further rabbits are being prepared with autolysates of these virulent meningococci, and others with the aqueous extracts of the same cocci after being dried and powdered. The value is also being determined of sensitizing the cocci, or its contents, before injection. By this means it is hoped to define the relative value of each of these preparations respectively of the same meningococcus for exciting the production of anti-endotoxin. It may be of interest to state that one rabbit that had received intravenously a dose of 0.1 c.cm. of the aqueous extract of a virulent example of Type I meningococcus prepared in the standard manner described previously, followed a week later by a dose of 0.2 c.cm., in spite of considerable loss of weight, showed on the sixteenth day after receiving the first dose sufficient anti-endotoxin in 0.5 c.cm. of its serum to neutralize completely a lethal dose of Type I endotoxin for the mouse. Captain Tulloch also found this serum to contain a good yield of opsonin for Type I. Here the matter at present stands.

CONCLUSION.

It would seem, then, that, as regards anti-endotoxin, there is at the present time much room for improvement in, at any rate, a considerable proportion of the samples of antimeningococcus serum supplied for therapeutic use. But it should be stated that several of these serums, though deficient in anti-endotoxin, have been found by Captain Tulloch, who is making a special study of meningococcus opsonins, to contain a good amount of opsonin which in the eyes of Flexner and some other authorities is of almost, if not quite, equal clinical importance. However this may be, few, I think, will deny that it is very desirable that all antimeningococcus serum sent out for therapeutic use as "multivalent" should contain as high a yield as possible not only of opsonins but also of anti-endotoxins capable of neutralizing the toxic principles of the commonest members of the meningococcus group.

The chief obstacle hitherto has been the absence of a trustworthy and simple procedure for determining the amount of anti-endotoxin in antimeningococcus serum. It is hoped that the present method may be found to contribute towards the end in view, because it would seem that some of the best results in the way of lowering the mortality from cerebro-spinal fever during the present outbreak have been obtained by early intrathecal administration of serum that, in addition to a good yield of opsonins, has also been found to contain an appreciable quantity of antibodies capable of neutralizing the endotoxins of each of the two commonest types of the meningococcus.

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NOTES ON ASTHMA.

BY

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GLASGOW.

SEVENTEEN years ago I put forward the view that asthma is in most cases essentially a toxæmia. More than once in this JOURNAL I have given arguments for this view and have amplified them in my book, and details will not be repeated, but some of the criticisms of that book and much recent writing show that that view is still far from being widely accepted, and yet the proof that asthma is a toxæmia is based not only on the clinical facts but on the best of all evidence—therapeutical success. Of 390 cases about 70 per cent. can fairly be reckoned as cured, or almost so. These cases have come from all parts of this country as well as from some of the colonies, so that "place" has less influence on asthma than was believed.

Among these 390 cases two groups become prominent clinically. One group is that of week-end asthma. The asthmatic attacks in working-class patients tend to appear at the week end, and are clearly associated with the over-feeding and under-exercise of the week end. I have

repeatedly dealt with this point. The only possible explanation of this periodicity is the upset metabolism resulting in a form of toxæmia which induces asthma. This class of case is usually, and for obvious reasons, readily amenable to treatment. This week-end periodicity is not confined to asthma or to man. It is found in some forms of albuminuria, angioneurotic oedema, and epilepsy; also in the "Monday morning disease" of horses (Woods Hutchinson). The toxæmia in this group is interesting as helping to explain the next group.

The second large group shows a clinical history of bronchitis in children, recurrent year after year, until ultimately what is called spasmodic asthma is diagnosed. The patient may be adolescent or adult before he realizes that he has asthma. In this class eczema is a prominent concomitant. Treatment proves this eczema and this asthma to be due to coddling, to confinement, and to carbohydrate excess, chiefly in the form of milk puddings; for alteration of these conditions means immediate improvement and ultimate cure of the diseases. Here again we have an imperfect metabolism leading to toxæmia, which, in turn, reveals itself in catarrh—of the skin as eczema: of the respiratory tract as various forms of rhinitis, enlarged adenoids, laryngismus stridulosa, bronchitis. This toxæmia acts not only on skin and mucous membrane, but, sooner or later, on the nervous system. And so the catarrhal condition may be accompanied or followed by a spasmodic state, hence—sometimes in combination—urticaria, angioneurotic oedema of the mucous membranes, laryngismus, paroxysmal sneezing, asthma.

Two points are of great importance in this connexion. First, the nose as the respiratory orifice, and the most sensitive area of the whole respiratory tract. If the nose is not right the lower mucous membrane is sooner or later likely to become affected by spasm as well as catarrh: hence, in treatment, attention must be directed to the nose as well as to the toxæmia. Secondly, the widespread connexion of the vagus with the digestive as well as with the respiratory tract has ever to be kept in mind. It is possible the vagus may be directly affected by the toxæmia. All this points to the importance of dietetic treatment, which Hyde Salter so rightly emphasized. Treatment of these two classes of cases is usually soon and absolutely successful; but where the toxæmia has lasted many years, and the mucous membrane has become so altered that *restitutio ad integrum* is not to be expected, the most we can hope for is improvement, though even here the spasmodic attacks may be abolished. I have seen recovery after twenty, thirty, and even forty years of asthma.

Consideration of the circumstances under which asthma arises in domesticated animals goes to support the view that it is a toxæmia. The subject is disappointingly dealt with in British veterinary textbooks, but the account in the American one by Law (1896) is excellent. What he says as to the origin of asthma in dogs and horses exactly bears out what I have written here and elsewhere as to its origin in man. Asthma in dogs "is almost exclusively confined to those kept indoors, over-fed, without exercise, plethoric, and constipated." Everyone is familiar with the wheezy, asthmatic pet pug, but is apt to miss the fact that it frequently belongs to a pampered mistress—fat, wheezy, and asthmatic for a like reason. Law continues: "The disease is one of pet dogs, kept in towns, deprived of exercise, of fresh air, and of the opportunity to relieve the bowels at will; and gorged with highly spiced meats and sweets at least three times a day. Sluggishness and obesity are marked characteristics of the dog when first attacked, though in the advanced stages the violence of the paroxysms and their frequent recurrence may have induced extreme emaciation." And Mr. Dan Hamilton, M.R.C.V.S., informs me that eczema in dogs is caused in precisely the same way. Similarly, Law connects asthma in horses directly with the feeding and want of exercise. Veterinary surgeons have often told me that it is possible to induce asthma in almost any colt by improper feeding. For the following instance I am indebted to Mr. Begg, veterinary surgeon to Lanark County Council. The case is too long to give except in summary; but the details all support the views stated:

A six-year-old van horse, which had cost £46, was seen in January, 1903, on account of asthma, was put in a loose-box, fed on soft oleaginous rations and damped fodder. By the end of March he was reduced to a skeleton—weak, staggering, and